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EXAMINER	
YOUNG, HUGH PARKER	
ART UNIT	PAPER NUMBER.
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/802,919	UNGER ET AL.	
	Examiner	Art Unit	
	Hugh P. Young	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/1/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Office Action

This is the first Office action on the merits of application 10/802,919. There is one claim pending and currently under consideration.

Elections/Restrictions

1. Applicant's election with traverse of Group VI from Restriction No. 1, drawn to a method for delivering protein into a cell *in vivo*, and Group I from Restriction No. 2, drawn to a method for using a halogenated alkyl chain to deliver a protein into a cell in the reply filed on August 21, 2006 is acknowledged. The traversal is on the ground(s) that restriction between Groups is not necessary because they are not so distinctly different as to be an undue burden to examine. This is not found persuasive because the main criteria in restricting, the location of the target cells (*in vitro* vs. *in vivo*) and the compounds to be delivered to the target cells both encompass widely divergent fields of art to be searched. In the former case cells *in vitro* can be subjected to a much wider array of chemical compounds than cells *in vivo*, mainly by virtue of the fact that in order to provide chemical compounds to cells *in vivo* the compounds and method of delivery must both be compatible with whole-organism pharmacological and physiological considerations, such as safety and tolerance by other cells in the organism as well as the possibility that the whole organism will reject or excrete the compounds in question. In regards the chemical compounds being delivered, the numerous types of bioactive molecules encompassed by the original claim set is so broad as to include compounds with greatly differing chemical structures and hence biochemical and physiological activities.

2. In light of the fact, however, that the different species of compounds to be delivered to cells *in vivo* are already known in the art to be physiologically and pharmacologically acceptable as well as being more amenable and accessible to being searched by the Examiner, the restriction to the delivery of only proteins to a cell in vivo is withdrawn, although the restriction to the target cells being in vivo is upheld.

3. The traversal of the restriction to Group I, Restriction No. 2, is not found persuasive because the array of compounds encompassed by the original claim set is so broad as to include types with widely divergent chemical structures and hence fields of search as well as differing biochemical and physiological properties.

The requirement is still deemed proper and is therefore made FINAL.

Objections to the claims

4. Claim 1 is drawn to non-elected subject matter in that applicant has recited elected compounds, including amines, ketones and ethers, that are not members of the elected group of halogenated alkyl chains. For this reason these compounds are not further addressed in this examination.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Stanko, G. L. (1962) in US Patent No. 3,039,929. Stanko discloses the use of various fluorinated

hydrocarbons in a formulation of isoproteronol and alcohol to be administered as a fine particle mist to patients in need of bronchodilation. In column 2, lines 7- 13 Stanko teaches that the physiologically active ingredient, isoproteronol, is soluble in short chain alchohols such as ethanol, which in turn is miscible with liquid, compressed-gas fluorinated hydrocarbons. These fluorinated hydrocarbons, of one or two carbons bound to fluorines and/or chlorines, are referred to by the brand names Freons, isotron, and Genetron. Example I, column 3, and Examples II and III, column 4, and Examples IV – X, columns 5 and 6, teach the use of Freon 11, 12 and 114 in particular. Stanko further teaches that the fluorinated hydrocarbons comprise "about 50% volume per volume of the final aerosol mixture." The use of liquefied fluorinated hydrocarbons in formulating the aerosol medicament is claimed in claims 1 – 10. The active ingredient, isoproteronol, is thus delivered to the epithelial cells of the bronchi and lungs in droplets of alcohol/fluorinated hydrocarbon. It can be appreciated that the droplets containing the bronchodilator contact the epithelial cells and that fluorinated hydrocarbons (organic halides) are therefore present at the time and place where the delivered compounds can be expected to enter the target cells.

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Harth H. et al. (1972) in US Patent No. 3,689,638. Harth et al. disclose the use of chloroform and enzymes in toothpaste formulations (column 6, line 58). It can be appreciated that the enzymes contained in the toothpaste will contact the epithelial cells and that chloroform (an alkyl halide) is therefore present at the time and place where the delivered protein enzymes can be expected to contact cells.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Cella J. A. et al. (1975) in US Patent No. 3,885,028. Cella et al. disclose the use of chloroform in toothpaste formulations (column 2, line 22) in which enzymes (amylases, dextranases, lysozyme, and proteases, such as pepsin, trypsin, chymotrypsin, papaine, bromeline, and bacterial or fungal proteases, lipases) and mixtures of such enzymes (column 1, lines 47-53). Harth also teaches (column 2, line 7) the use of polyvinyl chloride in toothpaste formulas that contain enzymes. It can be appreciated that the enzymes contained in the toothpaste will contact the epithelial cells and that chloroform and PVC (alkyl halides) are therefore present at the time and place where the delivered compound can be expected to enter the target cell.

9. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Grimm J. E. (1976) in US Patent No. 3,957,964. Grimm teaches the use of chloroform in toothpaste formulations (column 3, line 8) in which enzymes are formulated (column 5, lines 15). Grimm also teaches (column 2, line 48) the use of vinyl chloride, polyvinyl chlorides and polyvinylidene chlorides in toothpaste formulas that contain the enzymes. It can be appreciated that the enzymes contained in the toothpaste will contact the epithelial cells and that chloroform and VC/PVC components (alkyl halides) are therefore present at the time and place where the delivered compounds, including the enzymes, can be expected to contact epithelial cells.

10. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Pader M. (1979) in US Patents Nos. 4,152,418 and 4,178,362. Pader teaches the use of chloroform and enzymes in toothpaste formulations (Example 4; column 17, line 54-

column 18, line 42) disclosed in the '418 patent and similarly in the '362 patent. It can be appreciated that the enzymes contained in the toothpaste will contact the epithelial cells and that chloroform (an alkyl halide) is therefore present at the time and place where the delivered compounds, including the enzymes, can be expected to contact epithelial cells.

11. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Kraus, K. J. (1962) in US Patent No. 3,050,443. Kraus discloses the use of Freon 12 (dichlorodifluoromethane) in an aerosol preparation for headache relief. In column 3, lines 10-33, Kraus teaches that a surprising benefit of using Freon was that it allowed the reduction, but not elimination, of chloroform in the formulation for the aerosol droplets administered to the patient by inhalation. The active ingredient to be delivered in this medicament was spirits of ammonia, the two organic halides, chloroform and the fluoridated hydrocarbon Freon, being solvent carriers, and in the case of Freon, a propellant as well. It can be appreciated that Freon is completely miscible with chloroform and was thus present when the droplets of medicament contacted the epithelial cells in the bronchi and lungs of the patient. At the point of contacting the cell, any inherent properties the organic halides exert in aiding the penetration of the active ingredient would then come into play.

12. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Spero, B. (1963) in US Patent No. 3,073,743. Spero discloses the use of both fluorinated hydrocarbons (Freon) and chlorobutanol in compositions for delivering acetonide and other active ingredients to various tissues, including respiratory tissues by inhalation

and skin (cow udder) cells by lotion or ointment. Example 18, column 12, lines 51 –line 7, column 13, teach the use of two fluorinated hydrocarbons in formulating an metered-delivery aerosol preparation for treating asthmatic or allergic conditions. It can be appreciated that the fluorinated hydrocarbons, being miscible in the alcohol carrier, would be present at the point where the droplets contacted the epithelial cells lining the respiratory tract. Spero further teaches a similar application of fluorinated hydrocarbons in the same system, modified to deliver an active ingredient in powder form (Example 19, Column 13, lines 8-44). Finally, Spero teaches the use of the organic halide, chlorobutanol (anhydrous) in a topical preparation formulated for application to cows' udders to treat mastitis. The chlorobutanol, whatever its other properties or intended use, would be present and in contact with the epidermal cells of the udder and able to facilitate the penetration into the cells of the other active ingredients of the preparation. In U.S. Patent No. 3, 138,527 (1964) Spero teaches the use of the same organic halides used in analogous fashions to administer similar active ingredients to respiratory tissues (Examples 8 and 9) and to cows' udders (Example 10).

13. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Higuchi, T. (1975) in US Patent No. 3,891,757. Higuchi teaches the use of halogenated hydrocarbons in topical compositions comprising trichloroethanol and trifluoroethanol as solvents/penetrants (Abstract) and column 2, lines 2-10. In the list of suitable medicaments to be carried and delivered by these halogenated solvents Higuchi teaches "Protein drugs such as insulin" (item 1, column 3, line 26) as well as other bio-active species which encompass proteins and peptides, such as antigens and vaccines

(items 2 and 3, column 3). In addition Higuchi teaches (Examples 4 and 5, column 9, lines 10-23) the preparation of aerosol liquid sprays comprising trichlorofluoromethane and dichloro-difluoromethane in addition to the active ingredients and trichloroethanol. It can be appreciated that the chlorofluorocarbons will be miscible with the other components of the preparation and can be expected to be present in the droplets of applied material when it contacts the targeted epidermal cells. Furthermore, in claims 1 and 2 Higuchi claims the use of the penetrants trichloroethanol and trifluoroethanol with topical local anesthetics. It can be appreciated that chloroform is a topical anesthetic and can be so delivered.

14. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Jederstrom, G. L. (1974) in US Patent No. 3,823,229. Jederstrom teaches the use of fluorinated hydrocarbons in an inhalation composition of theophylline in an alcohol/water mixture (Examples 1 and 2, column 2 and Examples 2, 3, and 4, column 3, and Example 6, column 4). The use of fluoridated hydrocarbons is claimed in claim 1, column 4. It can be appreciated that fluoridated hydrocarbons are miscible in ethyl alcohol and would thus be present when the aerosol droplets contacted the epithelial cells of the respiratory tract. Jederstrom discloses (column 2, lines 59-64) that the particles have "excellent resorption properties in the respiratory tract."

15. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Cook, et al. (1977) in US Patent No. 4,044,126; Cook, et al. (1982) in US Patent No. 4,364,923; and Cook, et al. (1983) in US Patent No. 4,414,209. Cook et al. teach the use of organic halides, including methylene chloride, chloroform, and chlorofluorocarbons of 1-2

carbons in size (column 2, lines 44-67) for the making of solvated corticosteroid clathrates in order to make aerosol-deliverable microparticles of medicaments for respiratory delivery to patients. The use of halogenated hydrocarbons, in general, is taught in column 3, lines 21-25, of the 4, 044, 126 patent of 1977, but is recited throughout all three disclosures and claimed in claims 1, 4, 5, 6, 9, and 10. Organic halides are claimed as part of the pharmaceutical compositions of Patent 4, 364,923 in claims 1, 4, 5, 8, 10 and 12. Organic halides are claimed as components of the pharmaceutical compositions of Patent 4,414,209 in claims 1, 5, 6, 8, 9 and 10. It should be appreciated that in addition to the chlorofluoro- or fluorinated hydrocarbons the use of chloroform is claimed in claim 10 of the '209 patent.

16. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Witkowski, et al. (1980) in US Patent No. 4,211,771. Witkowski et al. teach the use of fluoridated hydrocarbons in a nasal spray composition for delivering an anti-viral agent to the respiratory tract. The use of various halomethanes, disclosed as brand names Freons 11, 12 and 14, is taught for delivering the active ingredient in a suitable solvent, in conjunction with surfactants such as fatty acids. It can be appreciated that both the solvents and surfactants are miscible with fluorinated hydrocarbons and the organic halides would thus be present when the aerosol droplets contacted the epithelial cells of the patients.

17. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Golub, et al. (1987) in US Patent No. 4,689,213. Golub et al. teach the use of fluoridated hydrocarbons in a nasal spray composition for delivering an calcium-channel blocking

agent to the respiratory tract. In colum 2, lines 4-7, Golub et al. teach that the active ingredient, gallopamil, can be dispersed in Freon itself and administered via a metered dose inhaler. It can be appreciated that the fluorinated hydrocarbons would thus be present when the aerosol droplets contacted the epithelial cells of the patients.

18. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Gwaltney, J. M. (1993) in US Patent No. 5,240,694. Gwaltney teaches the use of fluorinated hydrocarbons in delivering nasal/respiratory medicaments dissolved in the liquefied chlorofluorocarbons and delivered via a metered dose inhaler. In addition to the more commonly used Freons 11, 12, and 114, Gwaltney teaches (column 12, lines 24-36) the use of 1,1,1,2-tetrafluoroethan (HFC-134a) as being a more environmentally friendly carrier for the active ingredients. The aerosol droplets of halogenated hydrocarbons containing the active ingredients would impinge upon the epithelial cells of the nasal membranes with both organic halides and the active ingredients present, especially in light of Gwaltney's inclusion of lipophilic surfactants, including oleic acid, in the formulation. It can be appreciated that the presence of these lipids would aid in the retention of organic halides in the aerosol droplets and thus help provide organic halides to the recipient cell membranes.

19. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Gristina, et al. (1994) in US Patent No. 5,292,513. Gristina teaches the use of fluorinated hydrocarbons in delivering any phagocytosable, biocompatible particle to prime macrophages (Abstract), via a metered dose inhaler. In addition to the more commonly used Freons 11, 12, and 114, and perfluoropentane, Gristina teaches (column 11, lines

2850-36) the use of 1,1,1,2-tetrafluoroethan (HFC-134a) as being a more environmentally friendly carrier for the active ingredients. In this same paragraph Gristina teaches the advantages of using a lipophilic surfactant in the formulation, such as oleic acid. It can be appreciated that a lipophil such as oleic acid would retain organic halides in the aerosol droplets, along with any active components, which may themselves be lipophilic.

20. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Sarzaud, et al. (1996) in US Patent No. 5,558,664. Sarzaud et al. teach the use of fluorinated hydrocarbons in a dermal patch drug delivery device, in which the drug solution containing the active ingredient be mixed with Freon directly. The organic halides, Freons, would thus be presented to the targeted epidermal cells in concert with any molecules included as the active ingredients of the composition.

21. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Love, et al. (2002) in US Patent No. 6,436,368 B1. Love et al. teach the use of fluorinated hydrocarbons a Freon clathrate structure in claim 1, column 3, and claim 5, column 4. The formulation of this clathrate enables the delivery of the corticosteroid beclomethasone dipropionate via inhaler to asthmatics and sufferers of allergic rhinitis.

Double patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,638,767 B2. Although the conflicting claims are not identical, they are not patentably distinct from each other because it is obvious to simplify the method by deleting the step of applying ultrasound to the target cells or tissues. Futhermore, the nucleic acid DNA incorporates proteins, notably histones, into its structure and the introduction of proteins by use of organic halides is thus already encompassed by patent 6,638,757 B2.

Art of record

23. Higuchi, et al. (1987), US Patent No. 4,845,233, teach the use of halogenated urea compounds as dermal-penetrating adjuvants to be used instead of DMSO and DMA. In Column 3, lines 67-68 and column 4, lines 1-47, Higuchi et al. disclose the use of halogen substituents on cyclic urea compounds to make an agent for carrying physiologically active agents through body surfaces such as skin and mucous membranes. Higuchi et al. claim halogen substituted cyclic ureas in claim 1 and teach

their synthesis and use throughout their disclosure in addition to the initial citation above.

24. Rajadhyaksha V. J. (1976), US Patent No. 3,989,816, teaches that freons are "typical inert carriers" for use in pharmaceutical preparations (column 5, line 47) and Example 4 (lines 47-54), the latter application comprising Freon 114/12 as 75% of an aerosol formulation.

Conclusion

25. No claims are allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hugh P. Young whose telephone number is (571)-272-4988. The examiner can normally be reached on 8:00 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hugh P. Young Ph.D. GAU 1654